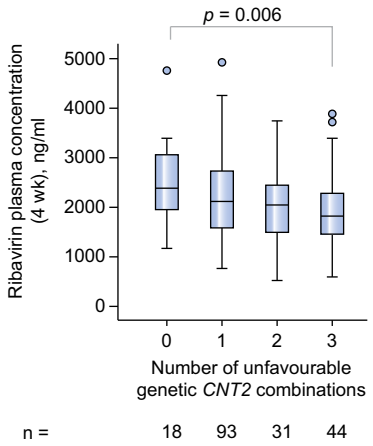

Fig. 1. Lower plasma concentrations of ribavirin were related to the higher number of "unfavorable" *CNT2* SNPs (rs11854484 [TT], rs2413775 [AT/TT] and rs1060896 [CC]). Only the difference between group "0" and "3" is statistically significant ($p = 0.006$).

predicted by week 2 concentrations, suggesting a possible early use of TDM to adjust the drug exposure both to enhance efficacy and reduce toxicity ($p < 0.001$) [9,10].

We therefore have no clear answer to the question as to whether genetic *SLC28* transporter polymorphisms predict ribavirin plasma levels. If RBV plasma exposure maintains its clinical impact in new anti-HCV treatment studies comparative evaluations of pharmacogenetics *vs.* early pharmacokinetics are warranted. It should also be highlighted that the cost of a single early (2 weeks) determination of ribavirin plasma concentration does not significantly impact on the overall expenditure associated with the use of (triple) anti-HCV therapy and may well contribute to a fruitful tailored management.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Rau M, Stickel F, Russmann S, Manser C, Becker P, Weisskopf M, et al. Impact of genetic SLC28 transporter and ITPA variants on ribavirin serum level, hemoglobin drop and therapeutic response in patients with HCV infection. J Hepatol 2013;58:669–675.
[2] D'Avolio A, Ciancio A, Siccardi M, Baietto L, Simiele M, Patanella S, et al. SLC28A2 65C >T predict sustained virological response in patients with hepatitis C treated with interferon and ribavirin, considering all HCV genotype and genotype 1/4. J Hepatol 2010;52:S463.
[3] D'Avolio A, Ciancio A, Siccardi M, Smedile A, Simiele M, Cusato J, et al. Negative predictive value of IL28B, SLC28A2 and CYP27B1 SNPs and low RBV plasma exposure for therapeutic response to PEG/IFN-RBV treatment. Ther Drug Monit 2012;34:722–728.
[4] Snoeck E, Wade JR, Duff F, Lamb M, Jorga K. Predicting sustained virological response and anaemia in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) plus ribavirin. Br J Clin Pharmacol 2006;62:699–709.
[5] D'Avolio A, Ciancio A, Siccardi M, Smedile A, Baietto L, Simiele M, et al. Inosine triphosphatase polymorphisms and ribavirin pharmacokinetics as determinants of ribavirin-associate anemia in patients receiving standard anti-HCV treatment. Ther Drug Monit 2012;34:165–170.
[6] D'Avolio A, Ciancio A, Siccardi M, Baietto L, Simiele M, Cariti G, et al. Ribavirin pharmacokinetics and interleukin 28B plus cytochrome P450 27B1 single-nucleotide polymorphisms as predictors of response to pegylated interferon/ribavirin treatment in patients infected with hepatitis C virus genotype 1/4. Hepatology 2011;54:2279.
[7] Aguilar Marucco D, Gonzalez de Requena D, Bonora S, Tettoni C, Bonasso M, De Blasi T, et al. The use of trough ribavirin concentration to predict sustained virological response and haematological toxicity in HIV/HCV-co-infected patients treated with ribavirin and pegylated interferon. J Antimicrob Chemother 2008;61:919–924.
[8] Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009;360:1839–1850.
[9] Caviglia G, D'Avolio A, Ciancio A, De Nicolò A, Boglione L, Abate M, et al. F-33 early ribavirin plasma concentration and ITPA polymorphisms as determinants of anemia after one month of anti-HCV therapy. Dig Liver Dis 2012;44:S42.
[10] Slavenburg S, Huntjens-Fleuren HW, Dofferhoff TS, Richter C, Koopmans PP, Verwey-Van Wissen CP, et al. Ribavirin plasma concentration measurements in patients with hepatitis C: early ribavirin concentrations predict steady-state concentrations. Ther Drug Monit 2011;33:40–44.

Antonio D'Avolio*
Jessica Cusato
Andrea Calcagno
Giovanni Di Perri
Unit of Infectious Diseases, University of Turin, Department of Medical Sciences, Amedeo di Savoia Hospital, Turin, Italy
*Corresponding author.
E-mail address: antonio.davolio@unito.it

Reply to: "Estimating ribavirin plasma exposure: Genetics or therapeutic drug monitoring?"

To the Editor:

We thank Dr. D'Avolio and colleagues for their critical comment on the measurement of ribavirin (RBV) plasma concentration during HCV therapy in general and its genetic basis in particular. This contribution adds further insight into the genetic basis of RBV bioavailability, which has been described in our study [1]. In their letter to the editor, D'Avolio *et al.* described an association between lower RBV plasma concentrations and a combination of "unfavorable" *CNT2* SNPs (rs11854484, rs2413775, rs1060896) in 186 HCV patients. Interestingly, an association between RBV plasma concentrations and rs11854484 alone was not seen as reported in our study [1]. Since our study included patients with a different RBV dosage, drug serum levels were adjusted to dosage. To address this issue in the study design, we analyzed only RBV serum levels at weeks 4 and 8 before eventual dose modification. As an alternative approach to account for drug dose adjustment in pharmacokinetic studies, D'Avolio *et al.* adjusted RBV concentrations for the dose pro kilogram and for dose reduction in their HCV positive patients. Although their findings did not exactly replicate the results of our study, the described association between lower RBV plasma concentrations and a combination of "unfavorable" *CNT2* SNPs must be taken as

another hint towards a functional role of SLC transporter polymorphisms for RBV bioavailability and related clinical outcomes. We agree that these genetic associations in heterogeneous studies with a limited patient number need further replication to strengthen the importance of the investigated SNPs.

Interestingly, our colleagues observed that RBV concentrations at week 2 have a predicting value for RBV concentrations at week 4. Therefore, early RBV serum measurement could help precocious adjustment of RBV dosage in HCV therapy. Most recent trials with direct-acting antiviral drugs indicate a continuous role of RBV in antiviral therapy regimens and further studies will clearly contribute to optimize RBV dosage. For routine clinical practice, comparative evaluations of pharmacogenetics versus early pharmacokinetics are rather dispensable in our opinion as drug level measurement will remain the key for clinical decision-making today. However, genetic studies like ours and the one of D'Avolio *et al.* contribute to the molecular understanding of pharmacokinetics and may guide the way towards a personalized HCV treatment strategy in the future.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Reference

[1] Rau M, Stickel F, Russmann S, Manser CN, Becker PP, Weisskopf M, et al. Impact of genetic SLC28 transporter and ITPA variants on ribavirin serum level, hemoglobin drop and therapeutic response in patients with HCV infection. J Hepatol 2013;58(4):669–675.

Monika Rau*
Andreas Geier
Division of Hepatology, Department of Medicine II, University Hospital Würzburg, Würzburg, Germany
*Corresponding author.
E-mail address: m.rau@medizin.uni-wuerzburg.de

"Wait and see" policy for early hepatocellular carcinoma

To the Editor:

We would like to comment on the recent article by Midorikawa and colleagues [1] about the management of early hepatocellular carcinoma (HCC). The authors suggest a "wait and see" policy when these lesions are recognized in a cirrhotic liver since the difference between the benefit of resection and observation was negligible in this subgroup of patients. In the authors' opinion, only overt HCC should be promptly treated whereas early HCC lesions should not be submitted to any form of therapy (including liver resection and percutaneous ablation) because of the treatment-related risks of liver function damage and severe complications. This clinical scenario parallels that of prostate cancer (PC): as it happens for small HCC detected during surveillance programs, more and more small volume tumoral foci are detected on prostatic biopsy ensuing Prostate Specific Antigen (PSA) screening [2]. Nowadays, deferred treatment in patients with insignificant disease has been advocated in the belief that radical prostatectomy is associated with significant morbidity and decrease in the quality of life whereas the majority of men are not at risk for dying of the disease, and that those who demonstrate disease progression can be identified and treated before the tumor becomes incurable [2]. As a consequence, over the last decade, active surveillance programs have gained popularity: in suitable candidates, stringent follow-up protocols including repeat biopsy are implemented so as to pick-up early tumoral progression [3]. However, similarities between HCC and PC clinical scenarios end at this point: the two tumors have different natural histories HCC carrying the worse prognosis and being superimposed on a chronic disease, which *per se* affects both patients' outcome and the decision as to whether or not to start a whatsoever form of treatment. This makes the window for curative therapy much narrower than in patients with PC. We agree that surgery (including resection and liver transplantation) represents an undue and costly overtreatment for an early HCC, but the same is not true for radiofrequency ablation (RFA). In our opinion, the Midorikawa's suggestion cannot be entirely shared since it relies on a misconception that surgery and local ablation are equivalent in terms of complications rate and capability of damaging liver function. To support their assumption they quote outdated and questionable references. In particular, the authors cite the article by Llovet *et al.* [4] where an exceedingly high rate of neoplastic seeding after RFA was reported. Those results, however, have been harshly criticized and a subsequent multicenter survey demonstrated clearly that, using a correct needle withdrawal technique, the seeding rate was far lower (less than 0.9% out of 1314 patients) and negatively affected only by a previous biopsy on the treated HCC nodule [5]. The authors seem to ignore that the worldwide use of RFA for HCC depends especially on its high efficacy in local control of the disease and lower invasiveness and costs when compared to surgery. In addition, there is recent evidence that RFA and resection offer similar results in terms of overall survival in case of HCC up to 3 cm emerging in well compensated cirrhosis [6,7].

One more drawback of an attendant approach for early HCC is that leaving a patients with an untreated cancer (even if small) poses other kinds of problems. Back to the parallelism with PC, the active surveillance is accepted by patients with reluctance as it is demonstrated by the low rate of enrollment in such protocols (not more than 30% of the suitable candidates) [2]. Several reasons can explain this finding: the inability to predict with absolute certainty favorable from unfavorable disease on an individual basis, the poor predictive markers of progression, and finally the difficulty of modifying the established standards of care. All these factors, including the psychological attitude of patients and the loss of the opportunity for cure during the surveillance period, should be taken into account in case of an active surveillance protocol for early HCC as suggested by Midorikawa *et al.*

It is not surprising that some urological groups are trying to apply the concept of local ablation in low-risk PC patients [8]. Local therapy might prove to be the middle ground for this subgroup of men, by combining acceptable cancer treatment with low morbidity.